

Supplementary information

Seasonal influence on respiratory tract infection severity including COVID-19 quantified through

Markov Chain modelling

Rob C van Wijk^{1,2}, Laurynas Mockeliunas¹, Caryn M Upton³, Jonathan Peter⁴, Andreas H Diacon³,
Ulrika S H Simonsson^{1*}

¹Department of Pharmaceutical Biosciences, Uppsala University, Sweden, ²Department of Bioengineering & Therapeutic Sciences, University of California, San Francisco, California, United States (current affiliation), ³TASK, Cape Town, South Africa, ⁴Department of Medicine, University of Cape Town Lung Institute and Division of Allergy and Clinical Immunology, University of Cape Town, Cape Town, South Africa * ulrika.simonsson@farmbio.uu.se

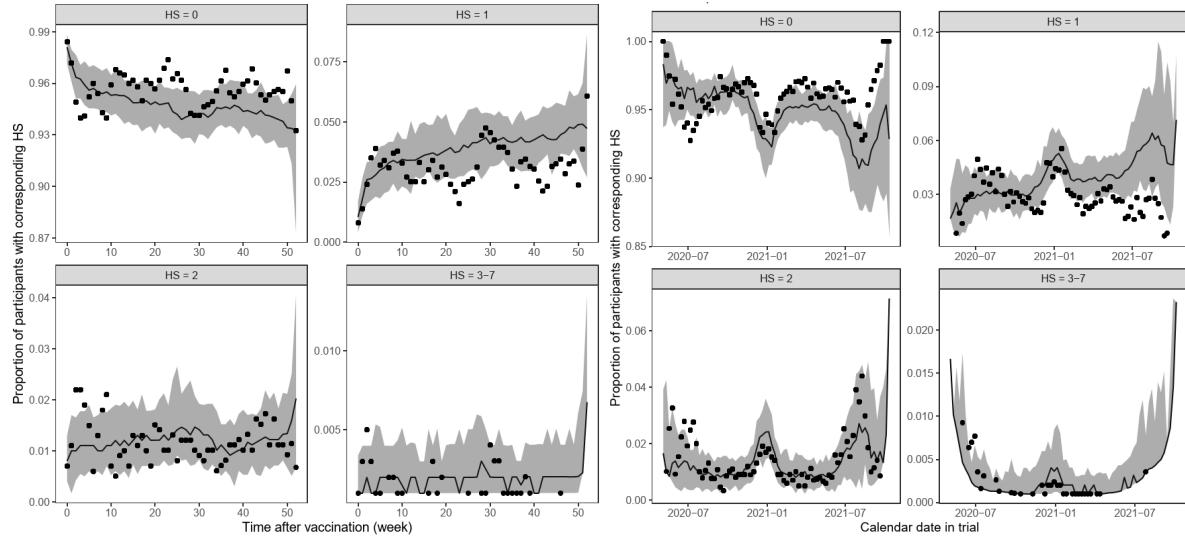


Figure S1. Simulation based diagnostics of the final covariate model of proportion of participants of the trial in health score (HS) 0 (healthy), 1 (mild symptoms), 2 (moderate symptoms), and 3-7 (severe symptoms and up) over time-in-trial (left) and calendar-time (right). Shaded area shows the 95% simulation interval, solid line shows the median from the simulation, and symbols are the observed proportions.

Table S1. Number of observed transitions between health scores with weekly resolution. Health scores:
healthy (0), mild symptoms (1), moderate symptoms (2), severe symptoms (3), hospitalization (4),
hospitalization with oxygen (5), hospitalization with ventilation (6), and death (7).

Final model code

```
;NONMEM v.7.5.0

;Author: Rob Christiaan van Wijk, PhD (ORCID: orcid.org/0000-0001-7247-1360)

$PROBLEM      Markov Chain for Respiratory Tract Infection Health Status

;Sim_start

$DATA        20220209_RW04_markov_dataset_epi2_v4.csv IGNORE=@
;$DATA        20220209_RW04_markov_dataset_epi2_SIM_v4.csv IGNORE=@

Sim_end

$INPUT        ID=DROP ID EVENT TIME DV SKIP PDV DELTAT SERO
CASEREL_OLD=DROP SEROBASE IGRABASE VAC VACID FLUVAC AGE GENDER BMI
HT WT ETHN JOB DM HYPTEENS ASTHMA CVD COPD OTHERLUNG KD BCGSCAR
PACKYEARS GROUP SITE EXPINTERACT SMOKING FIRSTPEAK CASEREL01 CASEREL
IGRACONV ETHN0 ETHN1 ETHN2 ETHN3 ETHN4 JOB0 JOB1 JOB2

$PRED

;Typical value

TVP01 = THETA(1)
TVP02 = THETA(2)
TVP03 = THETA(3)
TVP10 = THETA(4)
TVP12 = THETA(5)
TVP13 = THETA(6)
TVP20 = THETA(7)
TVP21 = THETA(8)
TVP23 = THETA(9)
TVP30 = THETA(10)
TVP31 = THETA(11)
TVP32 = THETA(12)

;Covariates
SLOPE_C19_P02 = THETA(13)
SLOPE_C19_P01 = THETA(14)
EXPON_C19_P03 = THETA(15)
SLOPE_C19_P21 = THETA(16)
```

```

VAC_P10      = THETA(17)
SERO_P02     = THETA(18)
SERO_P01     = THETA(19)
ETHN1_P10    = THETA(20)
GEN_P10      = THETA(21)
SEROBASE_P20 = THETA(22)
BCGTRT_P23   = THETA(23)
BCGTRT_P03   = THETA(24)

;create vaccination variable for covariate, 1 for either sars or flu
vac given

COVVAC = 0
IF(VAC.EQ.1) COVVAC = 1
IF(FLUVAC.EQ.1) COVVAC = 1

;Logit transformation

L01 = LOG(TVP01 / (1 - TVP01))
PL02 = LOG(TVP02 / (1 - TVP02))
PL03 = LOG(TVP03 / (1 - TVP03))
PL10 = LOG(TVP10 / (1 - TVP10))
PL12 = LOG(TVP12 / (1 - TVP12))
PL13 = LOG(TVP13 / (1 - TVP13))
PL20 = LOG(TVP20 / (1 - TVP20))
PL21 = LOG(TVP21 / (1 - TVP21))
PL23 = LOG(TVP23 / (1 - TVP23))
PL30 = LOG(TVP30 / (1 - TVP30))
PL31 = LOG(TVP31 / (1 - TVP31))
PL32 = LOG(TVP32 / (1 - TVP32))

;Covariate level

LGT01 = PL01 + CASEREL * (1 + (THETA(25) * FIRSTPEAK)) *
SLOPE_C19_P01 + SERO * SERO_P01
LGT02 = PL02 + CASEREL * (1 + (THETA(25) * FIRSTPEAK)) *
SLOPE_C19_P02 + SERO * SERO_P02
LGT03 = PL03 + ((CASEREL/0.00003612) * (1 + (THETA(25) *
FIRSTPEAK))) ** EXPON_C19_P03 + (GROUP - 1) * BCGTRT_P03 ;placebo
group 1 bcg group 2, median caserel in the dataset

```

```

LGT10 = PL10 + ETA(1) + COVVAC * VAC_P10 + ETHN1 * ETHN1_P10 +
GENDER * GEN_P10

LGT12 = PL12

LGT13 = PL13

LGT20 = PL20 + ETA(2) + SEROBASE * SEROBASE_P20

LGT21 = PL21 + ETA(3) + CASEREL * (1 + (THETA(25) * FIRSTPEAK)) *
SLOPE_C19_P21

LGT23 = PL23 + (GROUP - 1) * BCGTRT_P23 ;placebo group 1 bcg group 2

LGT30 = PL30

LGT31 = PL31

LGT32 = PL32

;Probability

P01 = EXP(LGT01) / (1 + EXP(LGT01))

P02 = EXP(LGT02) / (1 + EXP(LGT02))

P03 = EXP(LGT03) / (1 + EXP(LGT03))

P10 = EXP(LGT10) / (1 + EXP(LGT10))

P12 = EXP(LGT12) / (1 + EXP(LGT12))

P13 = EXP(LGT13) / (1 + EXP(LGT13))

P20 = EXP(LGT20) / (1 + EXP(LGT20))

P21 = EXP(LGT21) / (1 + EXP(LGT21))

P23 = EXP(LGT23) / (1 + EXP(LGT23))

P30 = EXP(LGT30) / (1 + EXP(LGT30))

P31 = EXP(LGT31) / (1 + EXP(LGT31))

P32 = EXP(LGT32) / (1 + EXP(LGT32))

;transition probabilities

T01 = P01

T02 = P02 * (1 - P01) ;fraction from remaining probability

T03 = P03 * (1 - P01 - (P02 * (1 - P01))) ;fraction from remaining
probability

T00= 1 - P01 - P02 * (1 - P01) - P03 * (1 - P01 - (P02 * (1 - P01)))

T10 = P10

T12 = P12 * (1 - P10) ;fraction from remaining probability

```

```

T13 = P13 * (1 - P10 - (P12 * (1 - P10))) ;fraction from remaining
probability

T11 = 1 - P10 - P12 * (1 - P10) - P13 * (1 - P10 - (P12 * (1 -
P10)))

T20 = P20

T21 = P21 * (1 - P20) ;fraction from remaining probability

T23 = P23 * (1 - P20 - (P21 * (1 - P20))) ;fraction from remaining
probability

T22 = 1 - P20 - P21 * (1 - P20) - P23 * (1 - P20 - (P21 * (1 -
P20)))

T30 = P30

T31 = P31 * (1 - P30) ;fraction from remaining probability

T32 = P32 * (1 - P30 - (P31 * (1 - P30))) ;fraction from remaining
probability

T33 = 1 - P30 - P31 * (1 - P30) - P32 * (1 - P30 - (P31 * (1 -
P30)))

;cumulative probabilities

CP00 = T00

CP01 = CP00 + T01

CP02 = CP01 + T02

CP03 = 1 - CP02

CP10 = T10

CP11 = CP10 + T11

CP12 = CP11 + T12

CP13 = 1 - CP12

CP20 = T20

CP21 = CP20 + T21

CP22 = CP21 + T22

CP23 = 1 - CP22

CP30 = T30

CP31 = CP30 + T31

```

```

CP32 = CP31 + T32
CP33 = 1 - CP32

;Sim_start

IF(PDV.EQ.0.AND.DV.EQ.0) Y = T00
IF(PDV.EQ.0.AND.DV.EQ.1) Y = T01
IF(PDV.EQ.0.AND.DV.EQ.2) Y = T02
IF(PDV.EQ.0.AND.DV.EQ.3) Y = T03

IF(PDV.EQ.1.AND.DV.EQ.0) Y = T10
IF(PDV.EQ.1.AND.DV.EQ.1) Y = T11
IF(PDV.EQ.1.AND.DV.EQ.2) Y = T12
IF(PDV.EQ.1.AND.DV.EQ.3) Y = T13

IF(PDV.EQ.2.AND.DV.EQ.0) Y = T20
IF(PDV.EQ.2.AND.DV.EQ.1) Y = T21
IF(PDV.EQ.2.AND.DV.EQ.2) Y = T22
IF(PDV.EQ.2.AND.DV.EQ.3) Y = T23

IF(PDV.EQ.3.AND.DV.EQ.0) Y = T30
IF(PDV.EQ.3.AND.DV.EQ.1) Y = T31
IF(PDV.EQ.3.AND.DV.EQ.2) Y = T32
IF(PDV.EQ.3.AND.DV.EQ.3) Y = T33

;----- simulation block -----
;

;    IF (ICALL.EQ.4) THEN
;        CALL RANDOM (2,R) ; generate a random number between 0 and 1
; (uniform distribution)
;
;    IF (NEWIND.NE.2) THEN ; reset for new individual
;        PREV = 0 ; everyone starts with HS0
;        DV = 0 ; observe HS0 at t=0

```

```

; PDVOUT = 0 ;output PDV
; ENDIF

;

; ;if the preceding DV is 0, allocate 0, 1, 2, 3 or higher
; IF (PREV.EQ.0) THEN
;     IF(R.LE.CP00) DV=0
;     IF(R.GT.CP00.AND.R.LE.CP01) DV=1
;     IF(R.GT.CP01.AND.R.LE.CP02) DV=2
;     IF(R.GT.CP02) DV=3
; ENDIF

;

; ;if the preceding DV is 1, allocate 0, 1, 2, 3 or higher
; IF (PREV.EQ.1) THEN
;     IF(R.LE.CP10) DV=0
;     IF(R.GT.CP10.AND.R.LE.CP11) DV=1
;     IF(R.GT.CP11.AND.R.LE.CP12) DV=2
;     IF(R.GT.CP12) DV=3
; ENDIF

;

; ;if the preceding DV is 2, allocate 0, 1, 2, 3 or higher
; IF (PREV.EQ.2) THEN
;     IF(R.LE.CP20) DV=0
;     IF(R.GT.CP20.AND.R.LE.CP21) DV=1
;     IF(R.GT.CP21.AND.R.LE.CP22) DV=2
;     IF(R.GT.CP22) DV=3
; ENDIF

;

; ;if the preceding DV is 3, allocate 0, 1, 2, 3 or higher
; IF (PREV.EQ.3) THEN
;     IF(R.LE.CP30) DV=0
;     IF(R.GT.CP30.AND.R.LE.CP31) DV=1
;     IF(R.GT.CP31.AND.R.LE.CP32) DV=2
;     IF(R.GT.CP32) DV=3
; ENDIF
;
```

```

;      ENDIF
;
;----- previous score -----
-----
;

;PDVOUT = PREV
;PREV = DV
;

;Sim_end

$THETA  (0,0.00917,1) ; P01
(0,0.00599,1) ; P02
(0,6.21E-05,1) ; P03
(0,0.402,1) ; P10
(0,0.0195,1) ; P12
(0,0.00468,1) ; P13
(0,0.282,1) ; P20
(0,0.603,1) ; P21
(0,0.0476,1) ; P23
(0,0.0435,1) ; P30
(0,0.455,1) ; P31
(0,0.5,1) ; P32
2580 ; SLOPE_C19_P02
1480 ; SLOPE_C19_P01
0.472 ; EXPON_C19_P03
-1470 ; SLOPE_C19_P21
-0.592 ; VAC_P10
-0.699 ; SERO_P02
-0.265 ; SERO_P01
0.67 ; ETHN1_P10
0.883 ; GEN_P10
1.23 ; SEROBASE_P20
1.17 ; BCGTRT_P23
0.804 ; BCGTRT_P03
(0,1.76) ; UNDERREP

```

```
$OMEGA 1.02 ; IIV_P10
1.05 ; IIV_P20
1 ; IIV_P21
;Sim_start
;
;$SIGMA 0 FIX ; DUMMY for simulation
;
$ESTIMATION METH=COND LAPLACE LIKE MAXEVAL=9999
$COV
$TABLE
;$SIMULATION (12345) (54321 UNIFORM) SUB=50 ONLYSIM
;$TABLE
;Sim_end
```